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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 11/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/780,041	KLEIN ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6-10,12-14 and 20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11 and 15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed August 19, 2002 (Paper No. 10) has been entered.

Applicants' election with traverse of Group I, Claims 1-5, 11, and 15-19 in Paper No. 10 is acknowledged. The elected invention is drawn to a method for producing a non-human animal model by transferring a gene encoding an aberrant form of tau, using somatic gene transfer techniques, a non-human animal comprising in its somatic cells a gene encoding an aberrant form of tau, and a method for inducing behavioral changes by somatic administration of a gene encoding an aberrant form of tau. The traversal is on the grounds that Groups I-IV should be examined together as the field of search for each invention is similar. This is not found persuasive because the inventions of Groups I-IV require separate searches, as they are directed to animals having distinct genetic modifications. Applicants argue that the method of the invention regards somatic gene transfer to a specific area of the brain of an organism to model neurodegenerative diseases. However, this is not an accurate characterization of the claimed invention. Claim 1 is directed to producing a model of any human or non-human animal disease, not a model of neurodegenerative diseases as Applicants assert here. Furthermore, only Claims 13-15 recite administering the gene expression construct to the brain and none of the claims regard somatic gene transfer to a specific area of the brain as Applicants assert here. Applicants further argue that in the interest of economy all 12 groups should be examined together. However, because the searches required for the separate inventions are not coextensive, a search and examination of all 12 inventions in a single application constitutes an undue burden. The restriction requirement is still deemed proper and is therefore made FINAL.

It is noted that Claims 1-3, 11, and 15-17 encompass non-elected subject matter. Thus, Claims 1-3, 11, and 15-17 are examined herein only to the extent that they encompass the elected subject matter.

Claims 1-22 remain pending in the instant application.

Claims 6-10, 12-14, and 20-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in Paper No. 10.

Accordingly, Claims 1-5, 11, and 15-19 are examined herein.

Drawings

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-5, 11, and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the final guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, Number 4, pp. 1099-1111 (also available at www.uspto.gov).

The claims are directed to a non-human genetically-modified animal comprising in its somatic cells a gene encoding an aberrant form of tau, wherein the animal is a model for a human or non-human animal disease and a method for producing said animal. However, the specification only describes genetically-modified rats that exhibit some features similar to those seen in Alzheimer's Disease. The claims are directed to a large genus of animals exhibiting any kind of phenotype associated with a disease of humans or other animals. However, the specification does not describe any other animal of the type claimed, wherein the animal exhibits a phenotype associated with a human or non-human animal disease. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, since phenotype cannot be predicted for a genetically-modified animal for the reasons discussed herein below and no working examples describe a genetically-modified animal or the type claimed, other than a rat having a specific pathologic phenotype, no genetically-modified animals other than rats have been described by their complete structure. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, since phenotype cannot be predicted from the gene being introduced, no identifying characteristics are provided for genetically-modified mice, primates, pigs, or any other animal. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of genetically-modified animals of the type claimed, other than rats having the specific pathologic phenotype

disclosed in the specification, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

Enablement

Claims 1-5, 11, and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rats genetically modified by administration of a viral vector encoding a mutant form of human tau comprising the P301L mutation, wherein the rats exhibit a neurofibrillary pathology as disclosed in the specification, methods of producing said rats by administration of a viral vector encoding a mutant form of human tau comprising the P301L mutation, and a composition comprising a viral vector encoding a mutant form of human tau comprising the P301L mutation, does not reasonably provide enablement for the broad scope of animals produced by transferring a gene encoding an aberrant form of tau as claimed nor the methods for producing said animals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification discloses rats that have been genetically modified by administration of an AAV vector encoding a mutant form of human tau (designated P301L tau in the specification). At page 14, lines 15-19, the specification discloses that the rats exhibit abnormal accumulation of tau in neuron cell bodies and dendrites, filaments immunoreactive for hyperphosphorylated tau, neuritic immunoreactivity for several antibodies that recognized neurofibrillary tangles in Alzheimer's and FTDP-17, and a dramatic increase of reactive astrogliosis.

The specification fails to provide an enabling disclosure for the preparation of the full scope of genetically-modified animals as claimed exhibiting an appropriate phenotype, other than genetically-modified rats, because the phenotype of a genetically-modified animal cannot be predicted.

The specification fails to provide an enabling disclosure for the preparation of any species of genetically modified animal harboring a gene encoding an aberrant form of tau because the guidance offered in the specification is not sufficient to teach one of skill in the art how to prepare the claimed genetically modified animals exhibiting an appropriate phenotype, other than rats. The mere capability to perform gene transfer in any given species is not enabling for the claimed genetically-modified animals and methods of producing them because the desired phenotype cannot be predictably achieved by simply introducing a construct as recited in the claims. While gene transfer techniques are well-developed for a variety of species, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. With regard to transgenic animals, the introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics and other *in vivo* genetic modifications is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct or no integration. When random integration occurs, insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant genetically-modified animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the genetically-modified animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a rat cannot necessarily achieve the same result in a mouse. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of genetically-

modified animals. Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000). In the absence of specific guidance, the production of a transgene-dependent phenotypic alteration resulting from the introduction of a nucleic acid construct as recited in the claim, is unpredictable. Thus, given the limited working examples directed exclusively to genetically-modified rats, the existence of any phenotypic alteration resulting from the introduction of a gene encoding an aberrant form of tau in any species of the animal kingdom other than rats, is highly unpredictable. Given the limited working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed genetically-modified animals over the full scope.

The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Houdebine (1994) discloses that in the field of transgenics, constructs must be designed case by case, without general rules, to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (page 275, column 1, paragraph 1). Wall (1996) discloses the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements, and may result in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Additionally,

Kappel et al. (1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, paragraph 4). The level of skill in the art of *in vivo* genetic modification is such that one cannot predict whether a transgene that is expressed in a mouse will also be expressed efficiently in another animal. For example, Strojek and Wagner (1988) point out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Furthermore, Wall (1996) explicitly teaches that transgene expression and the physiological consequences of transgene expression are not always accurately predicted in transgenic mouse studies (page 62, paragraph 1).

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention over the full scope. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of the genetically-modified animals as a model for Alzheimer's Disease, but the specification does not enable this use for any animal other than rats. The claims also cover the use of genetically-modified animals expressing an aberrant form of tau as a model for Huntington's Disease, but the specification does not enable this use for any animal species. In the absence of specific guidance for making and using genetically-modified animals other than rats exhibiting an appropriate phenotype, undue experimentation would have been required to make and use the full scope of the claimed animals and practice the claimed methods over the full scope.

Accordingly, given the demonstrated lack of predictability in the art, the limited amount of direction given, the state of the prior art, the quantity of experimentation needed, and the limited

applicable working examples, one of skill in the art would not be able to make and use the claimed invention over the full scope without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 11, and 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to -particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 11, and 15-17 are indefinite because the claims encompass non-elected subject matter.

Claims 1 and 17 are indefinite in their recitation of "appropriate tissue" because it is unclear what would constitute an "appropriate tissue."

Claims 4 and 18 are indefinite in their recitation of "wherein said at least one gene is an aberrant form of tau" because a gene cannot be an aberrant form of a protein; rather, genes encode proteins. Use of the claim language "wherein said at least one gene encodes an aberrant form of tau" is suggested.

Claims 5 and 19 are indefinite in their recitation of "P301L" because no reference sequence is provided and therefore it is unclear what numbering system is being used and which residue of tau is being referred to.

Claim 5 is indefinite in its recitation of "said aberrant form of tau" because the phrase lacks antecedent basis.

Claims 5 and 19 are indefinite in their recitation of "said aberrant form of tau is P301L" because the term "P301L" refers to a specific amino acid mutation and thus, an aberrant form of tau cannot be a single amino acid mutation.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER